Indinavir (IDV, Crixivan)

For additional information see Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Capsules: 100 mg, 200 mg, and 400 mg

Dosing Recommendations

Neonate/infant dose:
IDV is not approved for use in neonates/infants.

IDV should not be administered to neonates because of the risks associated with hyperbilirubinemia (kernicterus).

Pediatric dose:
IDV is not approved for use in children.

A range of IDV doses (234–500 mg/m^2 of body surface area) boosted by low-dose ritonavir (RTV) has been studied in children (see Pediatric Use).

Adolescent/adult dose:
800 mg IDV + 100 or 200 mg RTV every 12 hours.

Selected Adverse Events

- Nephrolithiasis
- Gastrointestinal (GI) intolerance, nausea
- Hepatitis
- Indirect hyperbilirubinemia
- Hyperlipidemia
- Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- Administer IDV on an empty stomach 1 hour before or 2 hours after a meal (or administer with a light meal). When given in combination with RTV, meal restrictions are no longer necessary.
- Adequate hydration is required to minimize risk of nephrolithiasis (≥48 oz of fluid daily in adult patients).
- If coadministered with didanosine (ddI), give IDV and ddI ≥1 hour apart on an empty stomach.
- IDV capsules are sensitive to moisture; store at room temperature (59–86°F) in original container with desiccant.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate.
- **Dosing in patients with hepatic impairment:** Decreased dosage should be used in patients with mild-to-moderate hepatic impairment (recommended dose for adults is 600 mg IDV every 8 hours). No dosing information is

available for children with any degree of hepatic impairment or for adults with severe hepatic impairment.

Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)***:***

- *Metabolism:* CYP3A4 is the major enzyme responsible for indinavir metabolism. There is potential for multiple drug interactions.
- Before indinavir is administered, the patient's medication profile should be carefully reviewed for potential drug interactions with indinavir.

Major Toxicities:

- *More common:* Nausea, abdominal pain, headache, metallic taste, dizziness, asymptomatic hyperbilirubinemia (10%), lipid abnormalities, pruritis, and rash. Nephrolithiasis/urolithiasis with indinavir crystal deposits.
- *Less common (more severe):* Fat redistribution.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, acute hemolytic anemia, and hepatitis (life threatening in rare cases).
- *Pediatric specific:* The cumulative frequency of nephrolithiasis is higher in children (29%) than in adults (12.4%).

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/IDV.html).

Pediatric Use: Indinavir has not been approved by the Food and Drug Administration (FDA) for use in the pediatric population. Even though indinavir was one of the first protease inhibitors (PIs) to be studied in children, its use in pediatrics has never been common and is currently very rare[1].

Both unboosted and ritonavir-boosted indinavir have been studied in HIV-infected children. Data in children indicate that a dose of 500–600 mg of unboosted indinavir per meter^2 of body surface area given every 8 hours results in peak blood concentrations and areas under the curve (AUC) slightly higher than those in adults but considerably lower trough concentrations. A significant proportion of children have trough indinavir concentrations less than the 0.1 mg/L value associated with virologic efficacy in adults[2-17]. Studies in small groups of children of a range of ritonavir-boosted indinavir doses have shown that 500 mg indinavir per meter^2 of body surface area plus 100 mg ritonavir per meter^2 of body surface area twice daily is probably too high[14], that 234–250 mg indinavir per meter^2 of body surface area plus low-dose ritonavir twice daily is too low[18-19], and that 400 mg indinavir per meter^2 of body surface area plus 100–125 mg ritonavir per meter2 of body surface area twice daily results in exposures approximating those seen with 800 mg indinavir/100 mg ritonavir twice daily in adults, albeit with considerable interindividual variability and high rates of toxicity[2,5,19].

As noted above, the cumulative frequency of nephrolithiasis is substantially higher in children (29%) than in adults (12.4%, range across clinical trials 4.7%–34.4%)[20]. This is likely due to the difficulty in maintaining hydration adequate to minimize risk of nephrolithiasis in children. Finally, a large analysis of more than 2,000 HIV-infected children from PACTG 219 demonstrated a hazard ratio of 1.7 for the risk of renal dysfunction among children receiving combination antiretroviral therapy (cART) with indinavir[21].

References

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